Debate: Adjuvant Immunotherapy is Superior in Stage II NSCLC

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Disclosures (past 3 years)

- Consulting & Advisory Board (no personal fees)
  - AstraZeneca, Genentech-Roche, Merck
- Institutional Research & Clinical Trial PI
  - AstraZeneca, Amgen, Genentech, Merck, Lilly, Pfizer, BMS, Spectrum, GSK, Iovance, CRISPR Therapeutics, BridgeBio, HotSpot Therapeutics, AdaptImmune

Added Disclosures…

- In the spirit of oncology debates, this presentation will involve:
  - Character assassination
  - Ad Hominem attacks
  - Questionable pop culture references to the 80s/90s

My Opponent – Dr. Jonathan Spicer

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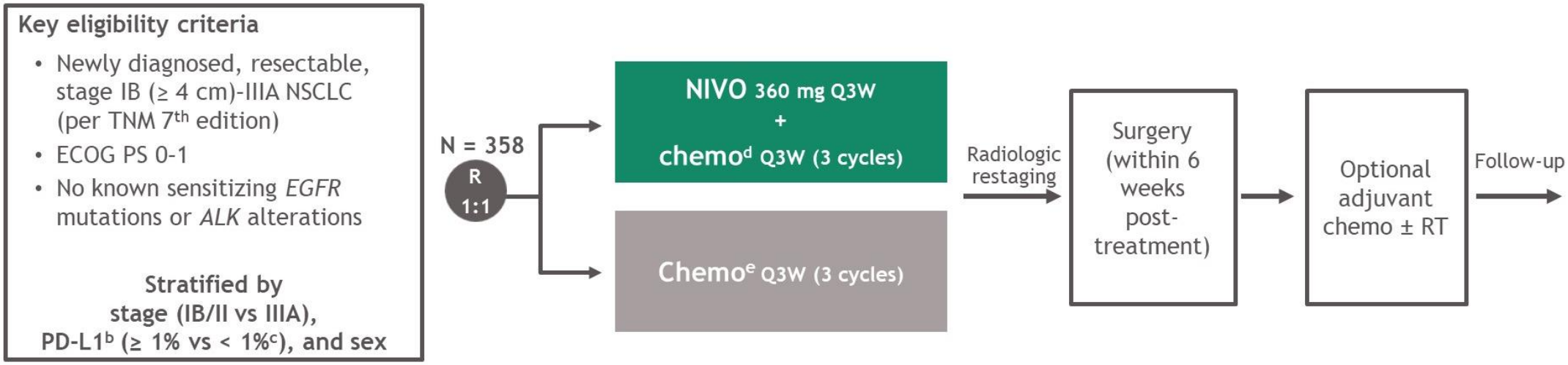
Approach to immunotherapy in resectable NSCLC

- Multiple rapidly evolving strategies involving resection
  - Neoadjuvant (CM816)
  - Perioperative (KN671, IMpower030)
  - Adjuvant (IMpower010, PEARLS)
- Alternatives for borderline resectable pts
  - ChemoRT + immunotherapy (PACIFIC)
- Alternatives for EGFR/ALK
  - ChemoRT then Osimertinib (LAURA)
  - Adjuvant TKI (ADAURA, ALINA)

Key considerations

- Upfront resectability
- Stage II vs Stage III
  - Stage II: node +ve vs node –ve
  - Stage III: single station N2 vs multi-station
- Tumor PDL1 status
- Tumor genomics

CM816 Design



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

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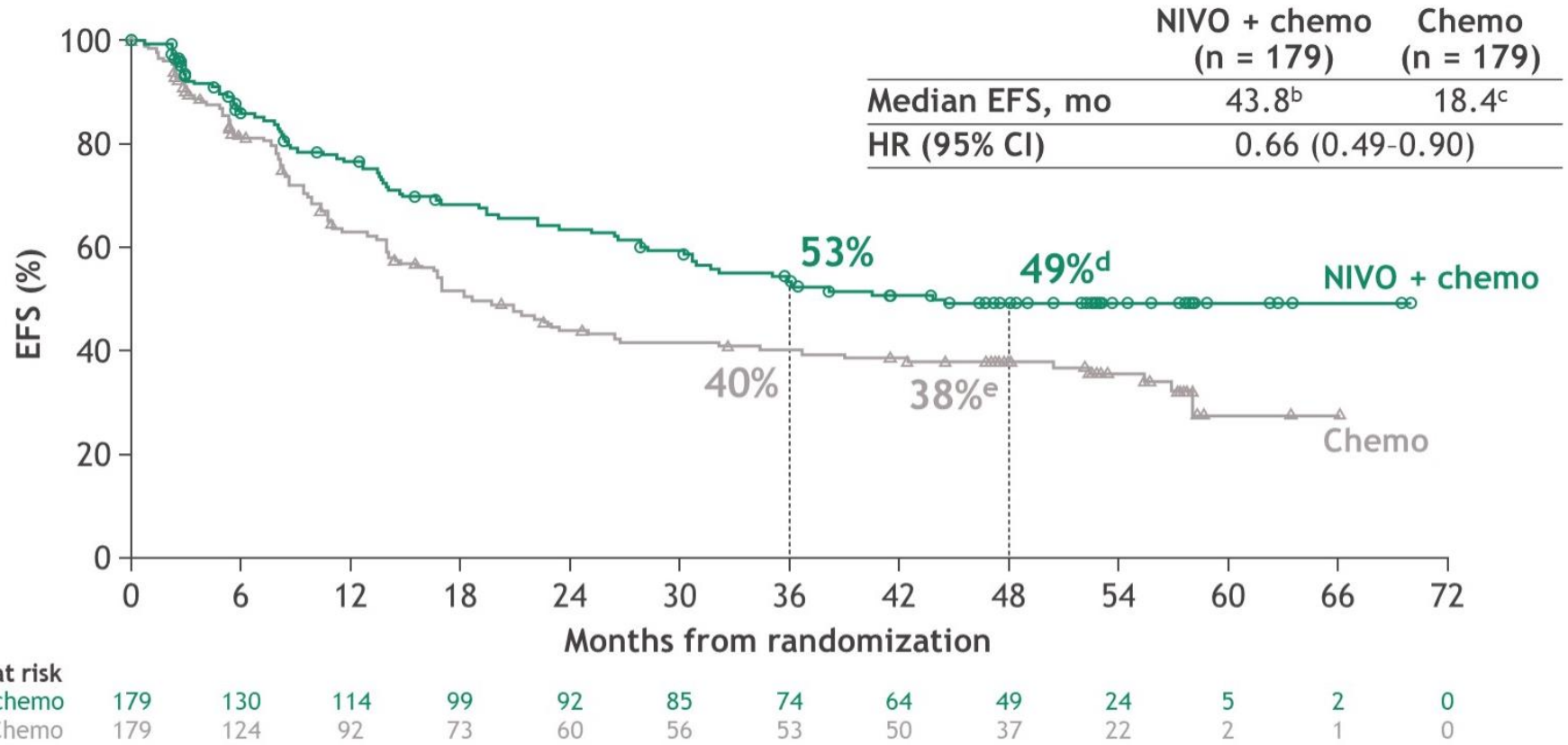
Spicer et al., ASCO Annual Meeting, 2021

CM816 Benefit



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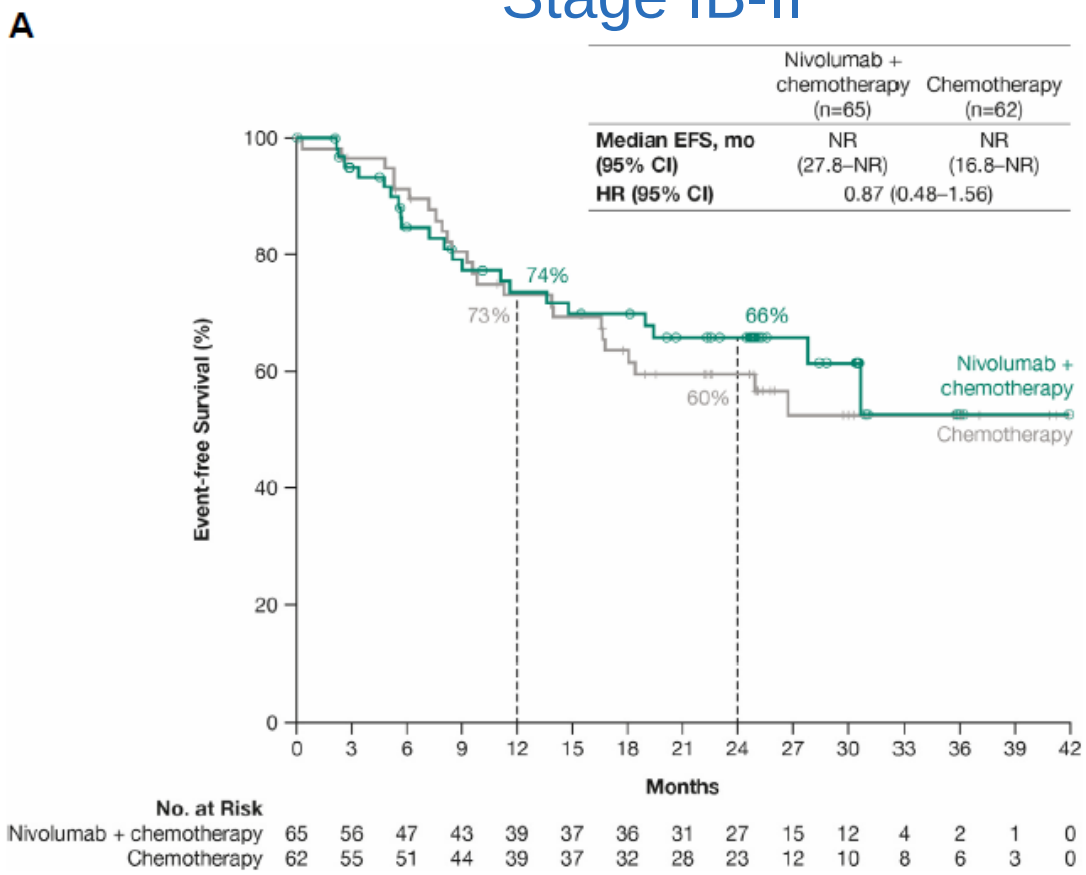
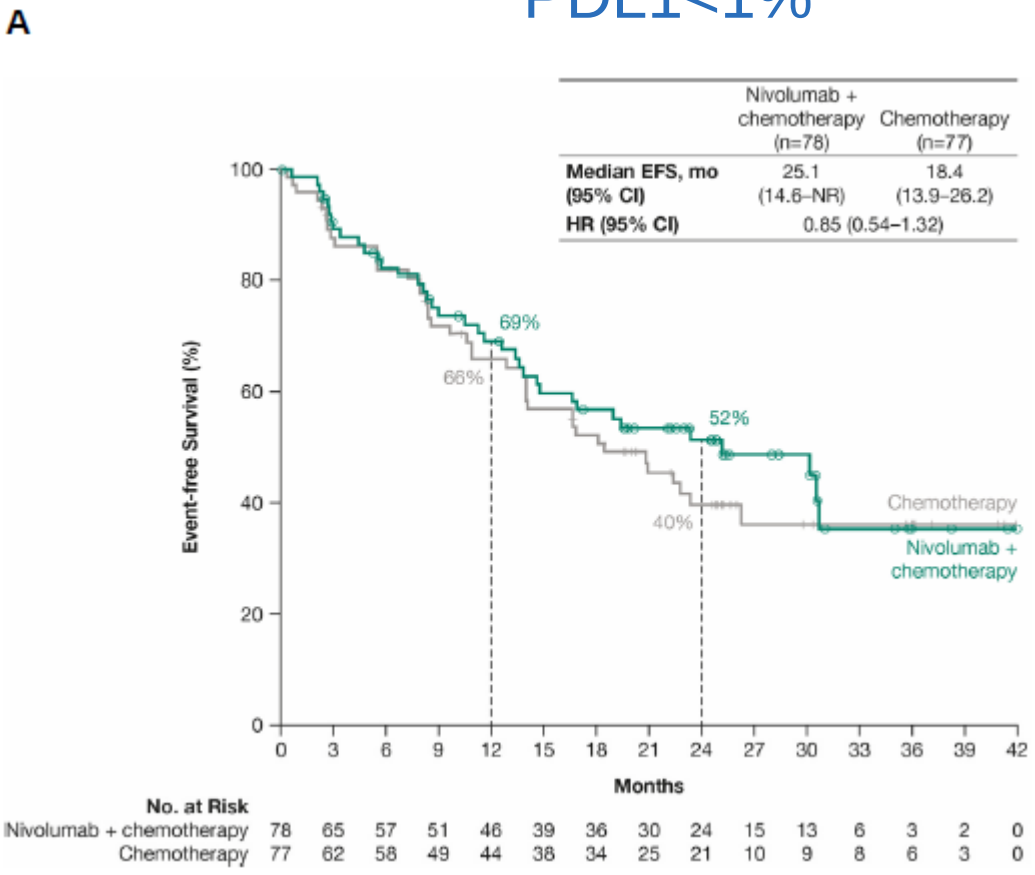
CM816 PFS in Key Subgroups

Stage IB-II



PDL1<1%



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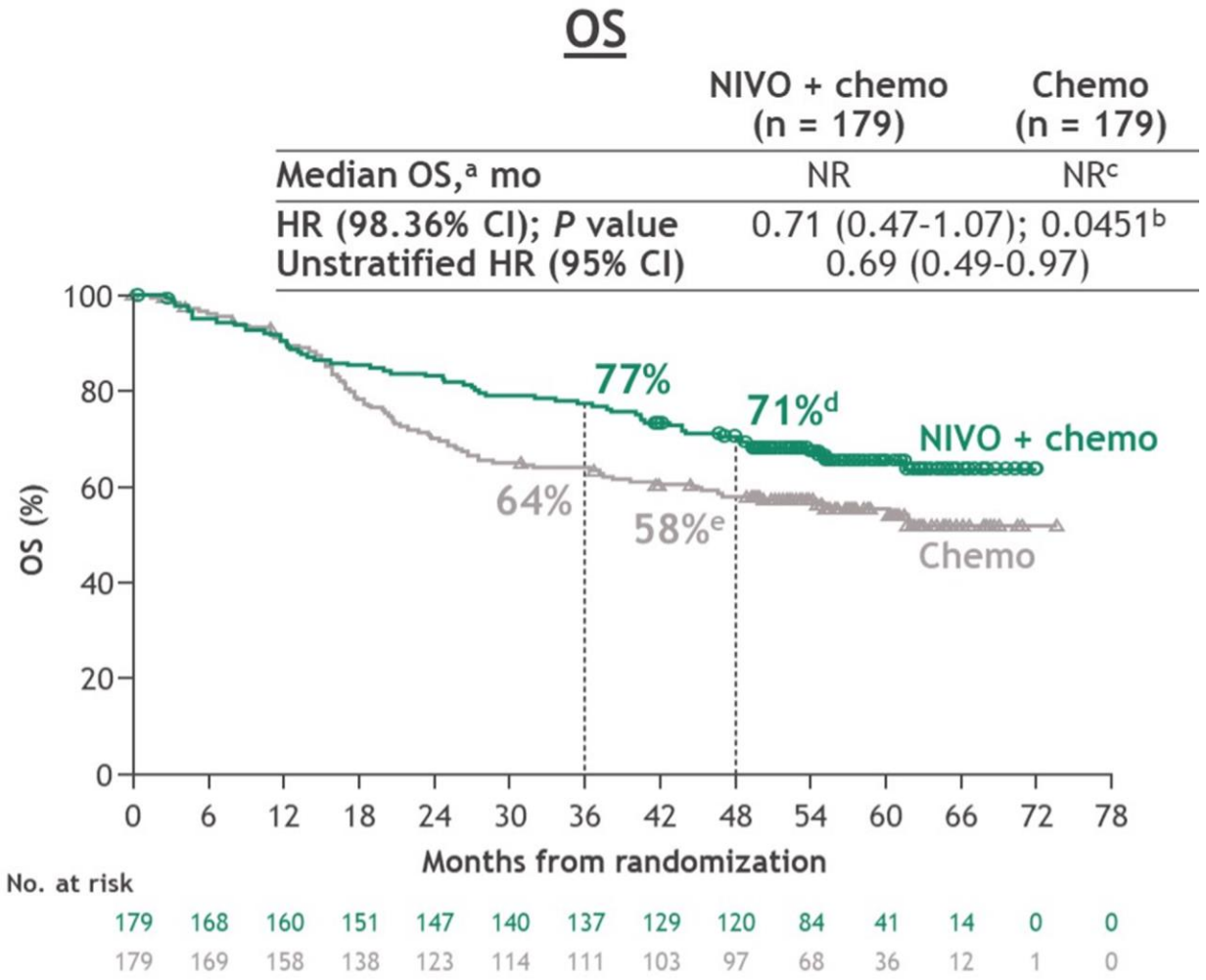
Forde et al., N Engl J Med, 2022

CM816 OS Trend



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CM816 Subsequent Therapy

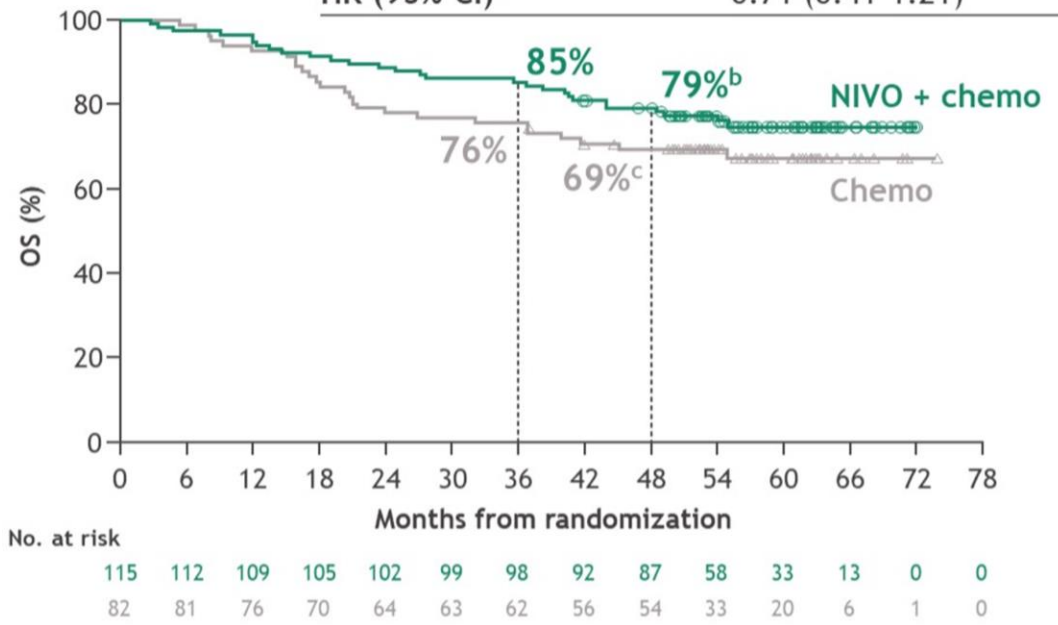
Patients, n (%)	Concurrently randomized patients		Patients with EFS events[b]	
	NIVO + chemo (n = 179)	Chemo (n = 179)	NIVO + chemo (n = 75)	Chemo (n = 101)
Any subsequent therapy	52 (29)	89 (50)	40 (53)	72 (71)
Radiotherapy	24 (13)	42 (24)	17 (23)	35 (35)
Surgery	5 (3)	9 (5)	5 (7)	7 (7)
Systemic therapy	44 (25)	75 (42)	33 (44)	63 (62)
Chemo	40 (22)	47 (26)	30 (40)	39 (39)
Immunotherapy	18 (10)	48 (27)	16 (21)	42 (42)
VEGFR inhibitors	12 (7)	16 (9)	11 (15)	15 (15)
EGFR/ALK TKIs	5 (3)	11 (6)	2 (3)	10 (10)
Other targeted therapy	0	4 (2)[c]	0	3 (3)[d]
Other systemic therapy	1 (1)	8 (4)	0	6 (6)

CM816 Surgical Resection

256 surgeries
but 358 pts?

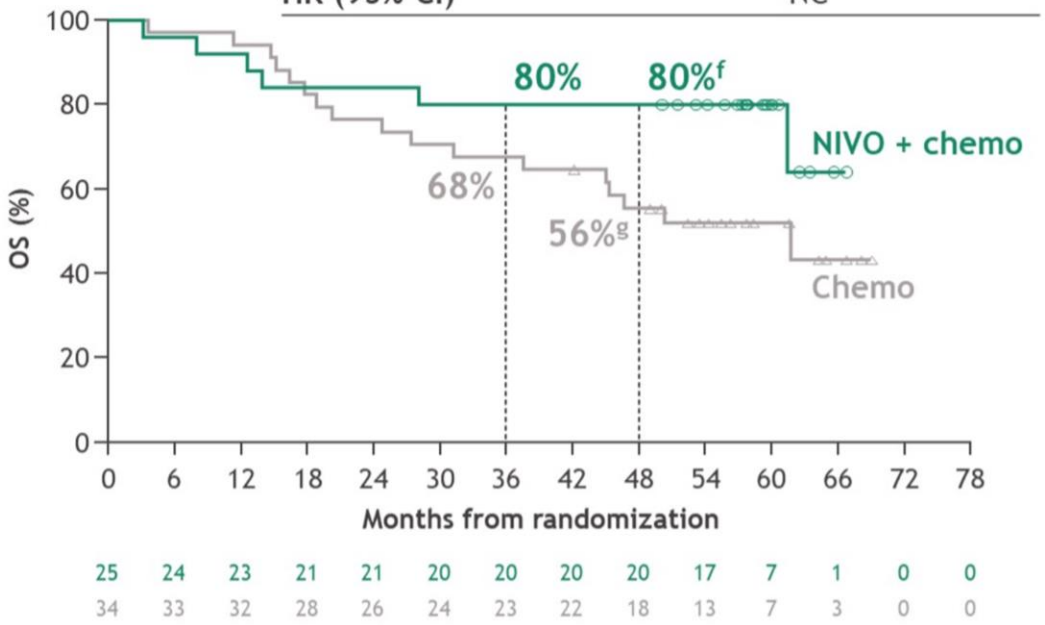
Lobectomy

	NIVO + chemo (n = 115)	Chemo (n = 82)
Median OS, mo	NR	NR
HR (95% CI)	0.71 (0.41-1.21)	



Pneumonectomy

	NIVO + chemo (n = 25)	Chemo (n = 34)
Median OS, mo	NR[d]	61.8[e]
HR (95% CI)	NC	



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WHERE IN THE WORLD
ARE
DR. SPICER'S MISSING PATIENTS?

Mysterious patient disappearances…

- Could the study have miscounted?
  - Unlikely
- Could Dr. Spicer have intentionally ignored these patients in his presentation?
  - Impossible!
- Where could 1-in-5 patients have gone?
  - Seemingly paranormal phenomenon…


To find the missing patients, you must go where surgeons fear to tread…


CM816
Supplementary
Data

CM816 – approximately 1-in-5 patients do not make it to the OR

	Stage IB–II	
	Nivolumab plus Chemotherapy (N = 65)	**Chemotherapy (N = 62)**
Patients with definitive surgery* — no. (%)	55 (84.6)	52 (83.9)
Patients with cancelled definitive surgery — no. (%)	8 (12.3)	8 (12.9)
Disease progression	3 (4.6)	1 (1.6)
Adverse event	0	0
Other†	5 (7.7)	7 (11.1)
Patients with delayed surgery‡,§— no. (%)	9 (16.4)	13 (25.0)
Administrative reason	4 (7.3)	4 (7.7)
Adverse event	2 (3.6)	7 (13.5)
Other	3 (5.5)	2 (3.8)

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Forde et al., N Engl J Med, 2022

What Proportion of Patients Underwent Surgery in Neo-Adjuvant Trials?

Trial	No. of pts*	No Surgery	%
I-0139	202	164	81%
NATCH	199	181	91%
LU-22	258	230	89%
ChEST	129	112	87%
S9900	190	152	80%
DePierre	179	167	93%
Total	1157	1006	87%

**In the neo-adjuvant arm*

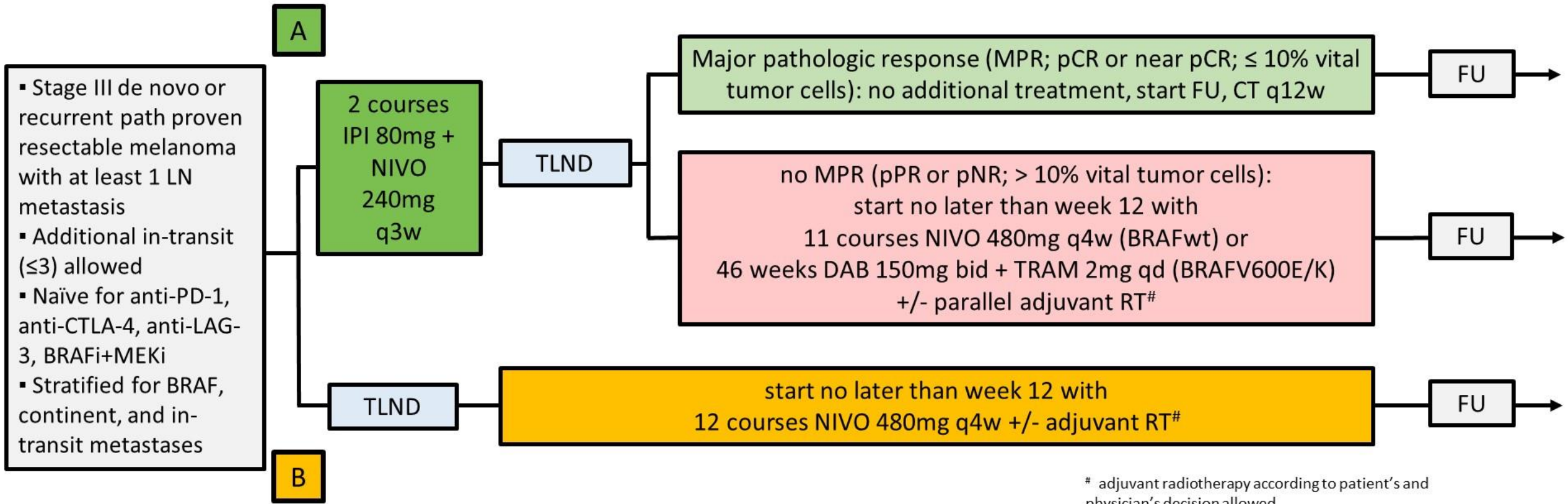
Slide courtesy of Dr. Shepherd

What Proportion of Patients Underwent Surgery in Neo-Adjuvant IO Trials?

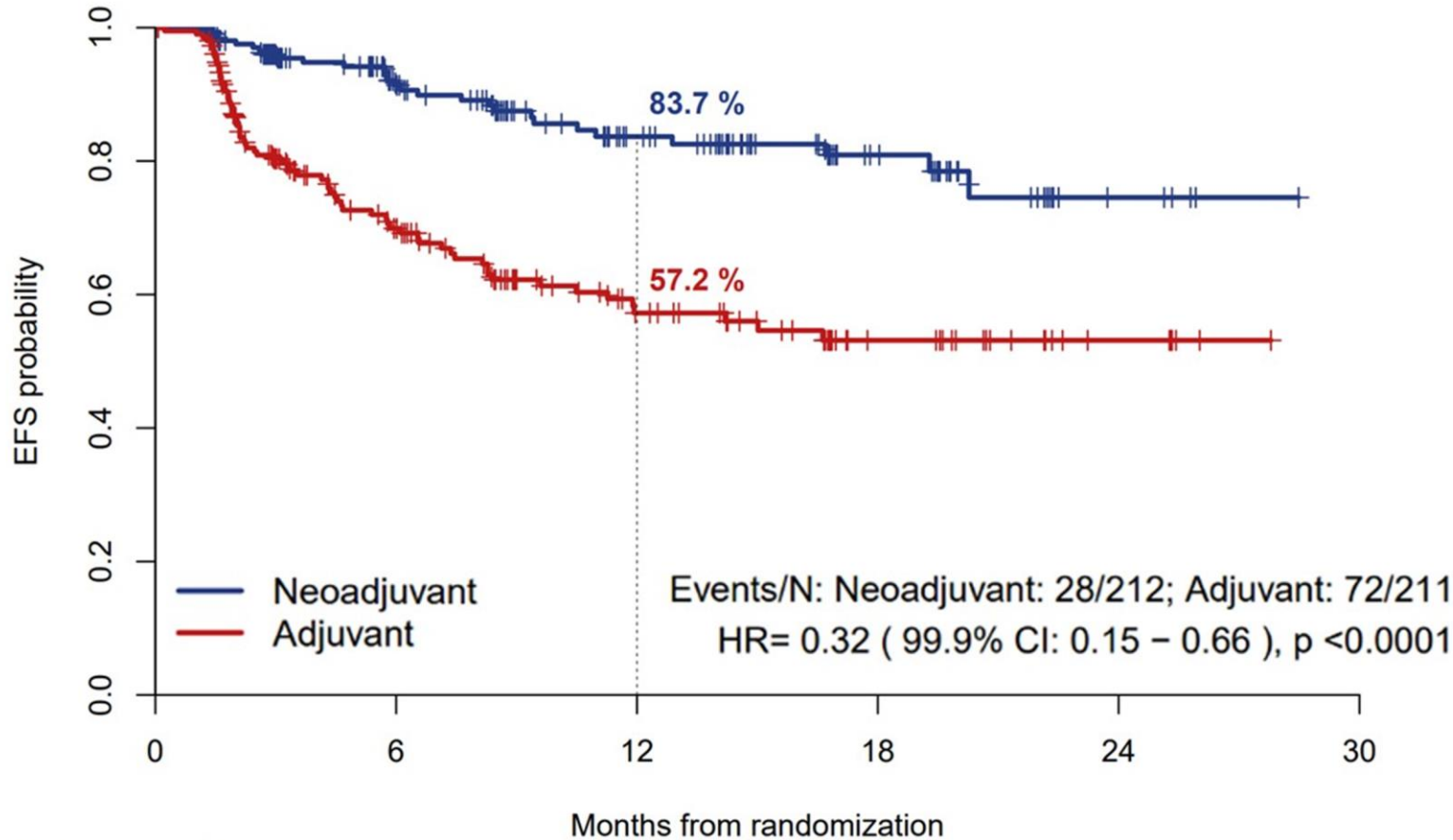
Trial	No. of pts	No Surgery	%
Keynote 671 Pembro	397	325	82%
Keynote 671 Placebo	400	317	79%
CM816 CT	179	134	75%
CM816 Nivo-CT	179	148	83%
Total	1247	1003	80%

Slide courtesy of Dr. Shepherd

NADINA - Trial Design

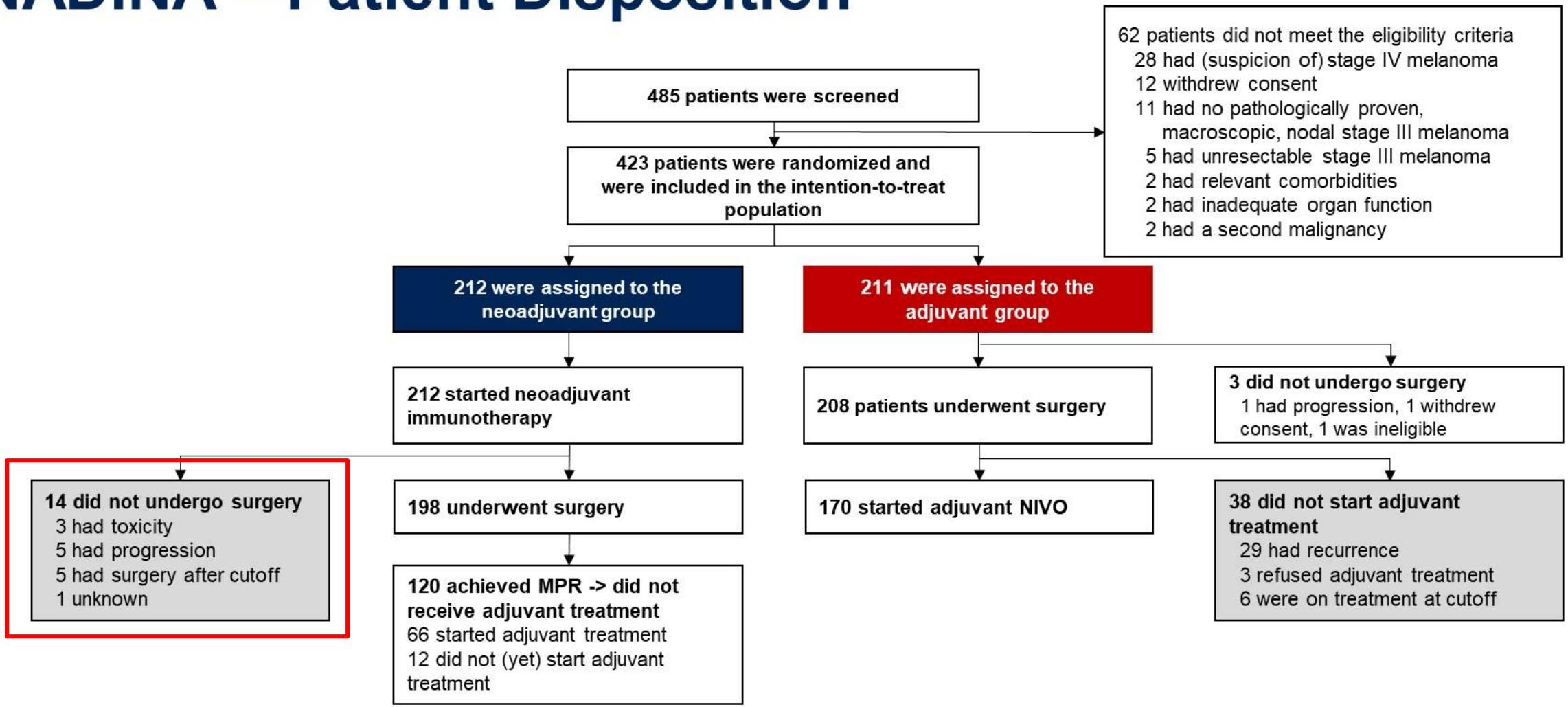


NADINA – Primary Endpoint: Event-Free Survival (EFS)



# at risk (censored)										
Neoadjuvant	212	(0)	126	(71)	77	(111)	34	(152)	5	(179)
Adjuvant	211	(0)	100	(57)	53	(89)	23	(116)	6	(133)

NADINA – Patient Disposition



At data cut-off (January 12, 2024) with a median follow-up of 9.9 months, 99 patients were still on treatment (31 neoadjuvant, 68 adjuvant arm)

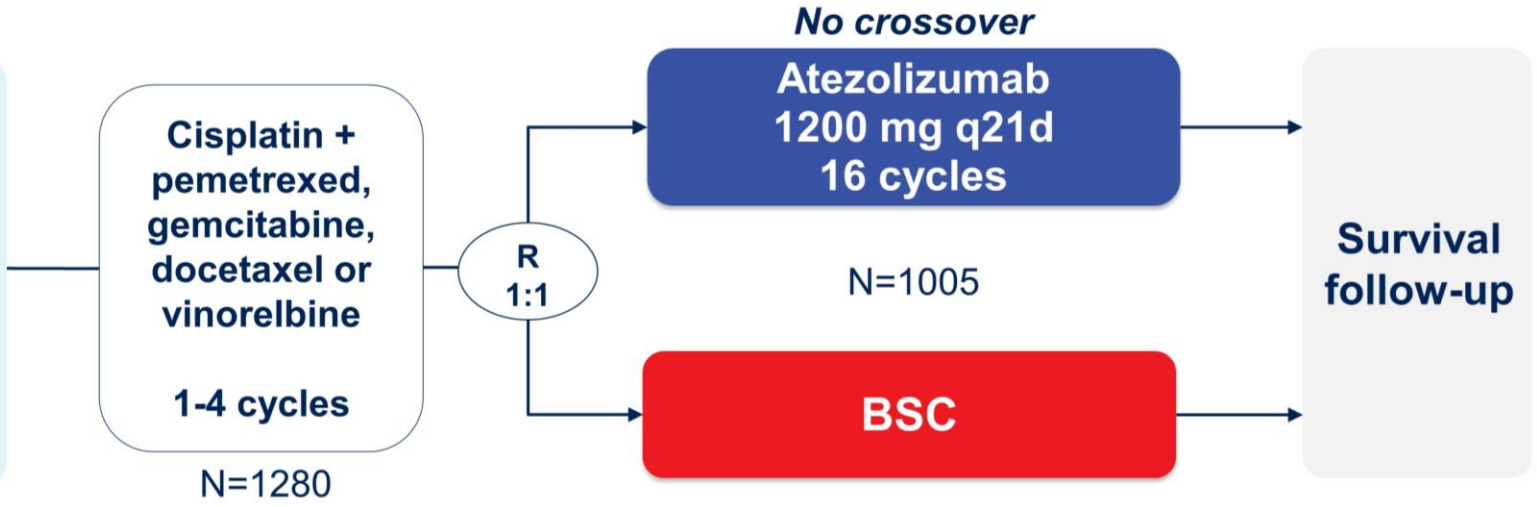
Neoadjuvant Chemo-Immunotherapy in Stage II NSCLC

- **1-in-5** patients do not make it to the OR
- Benefit of immunotherapy in stage II patients is modest
- No randomized data in resected NSCLC comparing neoadjuvant vs adjuvant vs perioperative approach
  - Comparison to melanoma in stage II NSCLC not appropriate
- Adjuvant chemo-immunotherapy represents a compelling alternative

IMpower010

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

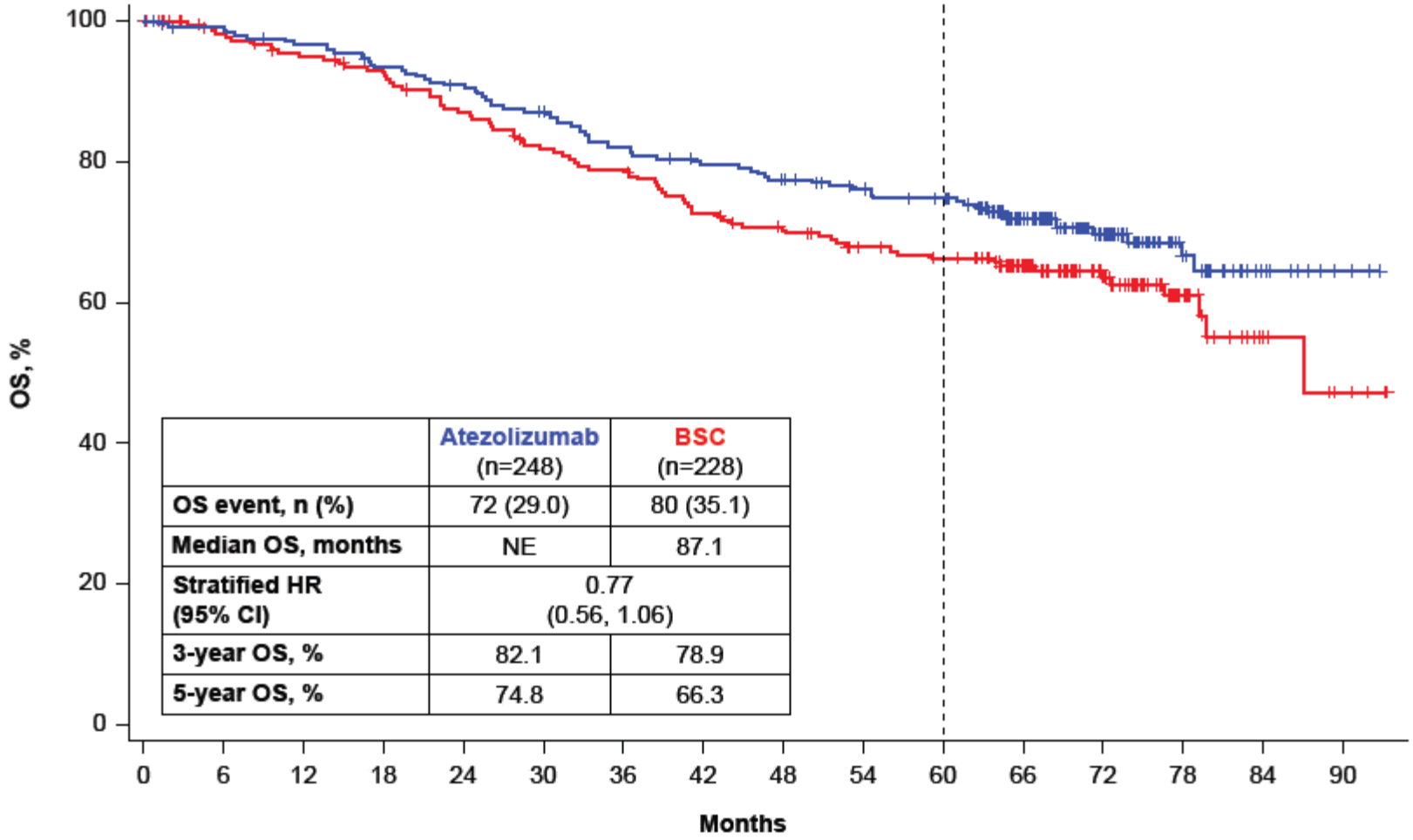
- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

IMpower010 PDL1≥1%



	Atezolizumab (n=248)	BSC (n=228)
OS event, n (%)	72 (29.0)	80 (35.1)
Median OS, months	NE	87.1
Stratified HR (95% CI)	0.77 (0.56, 1.06)	
3-year OS, %	82.1	78.9
5-year OS, %	74.8	66.3

No. at risk																
Atezolizumab	248	241	234	225	218	208	195	187	181	173	167	126	76	32	11	3
BSC	228	214	205	198	185	172	166	152	144	134	129	103	65	29	9	4

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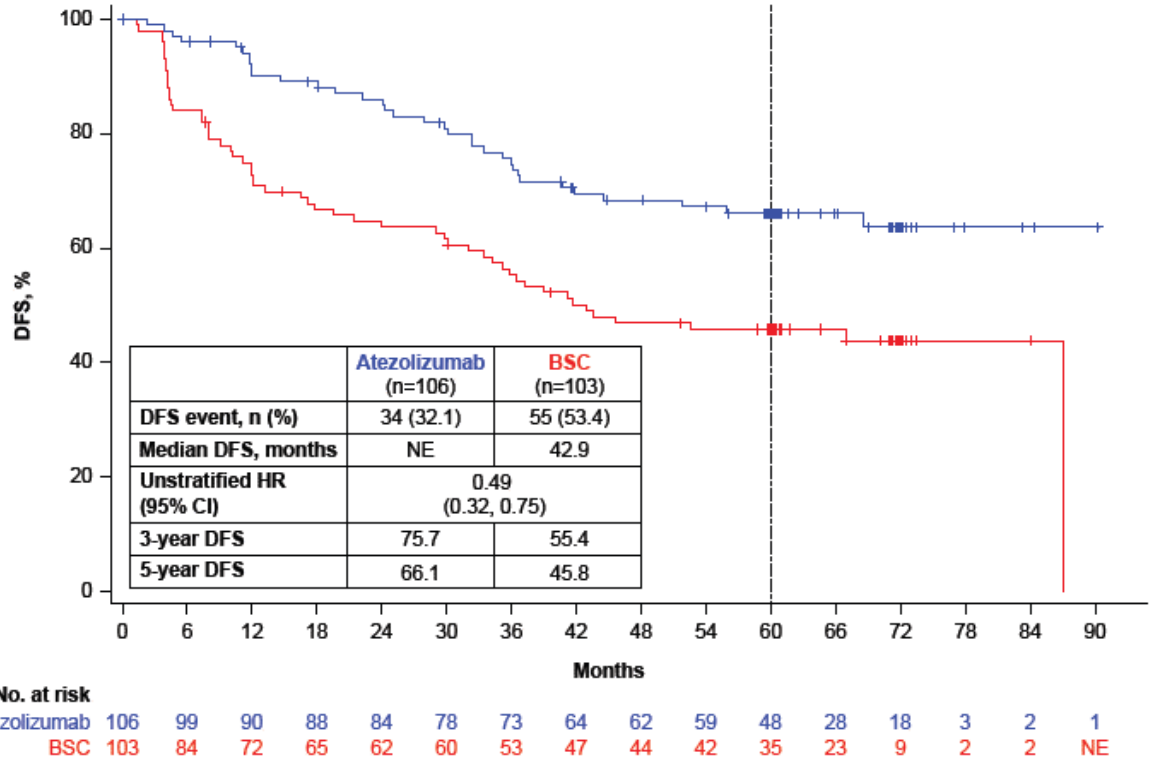
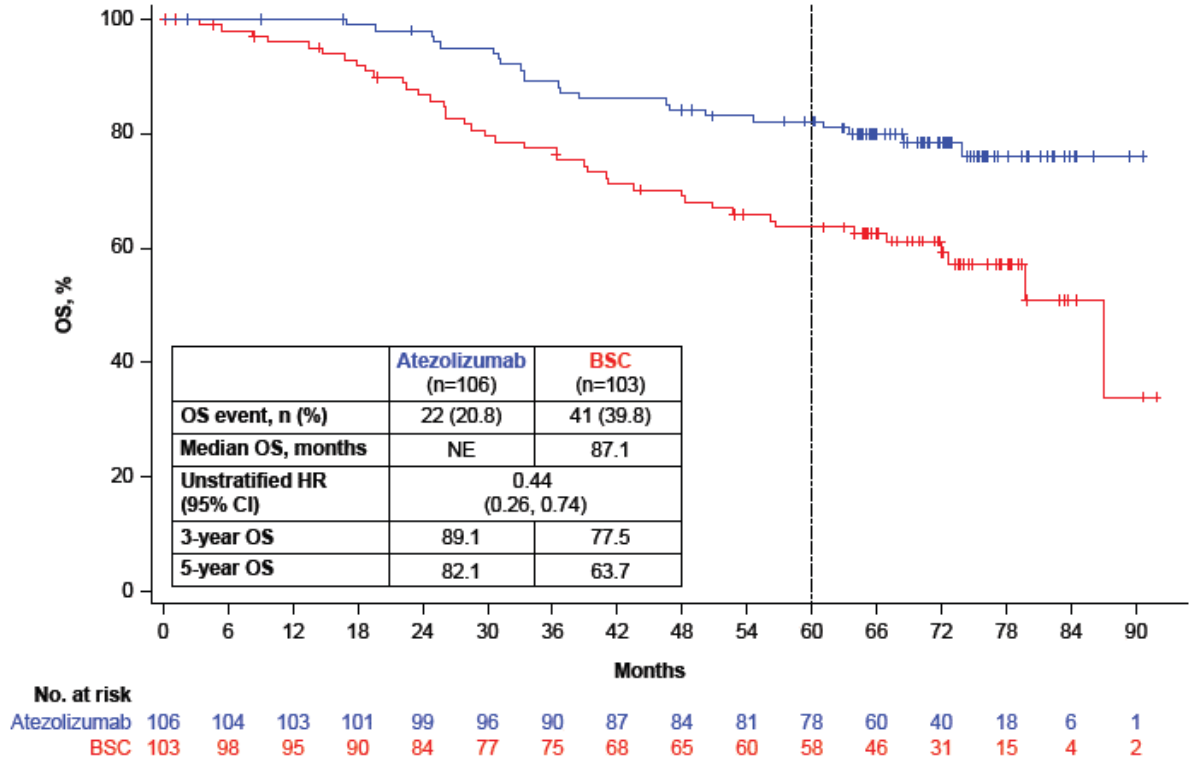
Wakelee et al., ASCO Annual Meeting 2024

IMpower010 PDL1>50%





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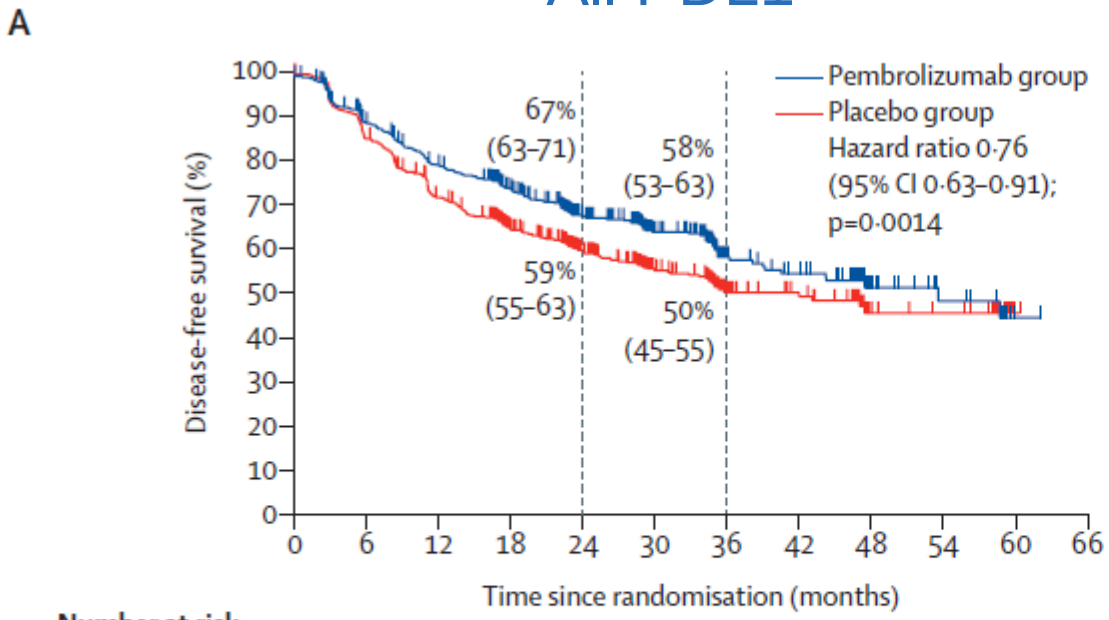
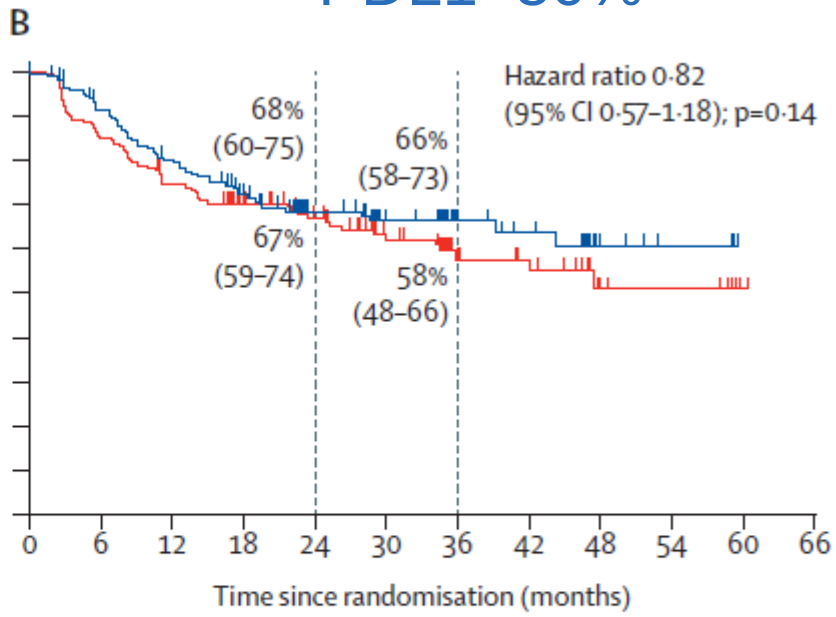
PEARLS/KN091

All PDL1



PDL1>50%



Number at risk (number censored)												
Pembrolizumab	590	493	434	358	264	185	82	70	28	16	1	0
	(0)	(30)	(36)	(84)	(150)	(216)	(306)	(313)	(352)	(363)	(377)	(378)
Placebo	587	493	409	326	241	160	72	57	22	18	1	0
	(0)	(5)	(13)	(56)	(118)	(183)	(259)	(273)	(305)	(309)	(326)	(327)

Pembrolizumab	168	145	126	99	69	50	26	22	7	4	0	0
	(0)	(8)	(9)	(24)	(49)	(66)	(90)	(93)	(107)	(110)	(114)	(114)
Placebo	165	140	121	100	75	54	28	22	8	6	1	0
	(0)	(0)	(2)	(16)	(37)	(53)	(76)	(81)	(94)	(96)	(101)	(102)

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O'Brien et al., Lancet Oncol., 2022

Adjuvant Chemo-immunotherapy in stage II NSCLC

- All patients undergo surgery including subsets less likely to benefit from immunotherapy
  - Reduced likelihood of delays due to toxicity or logistics as well
- Clear DFS benefit and increasing evidence of OS benefit
- No data suggesting neoadjuvant or perioperative approaches superior
  - Randomized studies desperately needed
- *All patients achieve a CR with surgery*

Conclusion

Take-home points

- **1-in-5** patients do not make it to the OR with neoadjuvant chemoimmunotherapy
- Clear DFS benefit and increasing evidence of OS benefit with adjuvant chemoimmunotherapy
- No randomized data in stage II NSCLC comparing neoadjuvant vs adjuvant vs perioperative approach
- Randomized studies desperately needed in resectable NSCLC


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